(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 127 581 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
15.06.2005 Bulletin 2005/24

(51) Int Cl.7: A61L 27/36, A61K 35/32, A61L 24/00

(21) Application number: 00301370.3

(22) Date of filing: 22.02.2000

(54) Malleable paste for filling bone defects

Verformbare Paste zum Füllen von Knochendefekten

Pâte malléable pour remplir des défauts osseux

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

(43) Date of publication of application:
29.08.2001 Bulletin 2001/35

(60) Divisional application:
04077080.2 / 1 477 176

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(56) References cited:
EP-A- 0 522 569
EP-A- 0 784 985
WO-A-98/14222
WO-A-99/11298
WO-A-99/52572
US-A- 5 314 476
US-A- 5 516 532
US-A- 5 707 962
US-A- 5 910 315
US-A- 6 030 635

Printed by Jouve, 75001 PARIS (FR)

EP 1 127 581 B1

Description

FIELD OF INVENTION

[0001] The present invention is generally directed toward a surgical bone product and more specifically is a flowable gel and a malleable putty based on demineralized allograft bone particles mixed in a fluid carrier comprising a hydrogel, in particular sodium hyaluronate.

BACKGROUND OF THE INVENTION

[0002] Malleable putty is used to correct surgical defects that may be caused by trauma, pathological disease, surgical intervention or other situations where defects need to be managed in osseous surgery. It is important to have the defect filler in the form of a stable, viscous putty to facilitate the placement of the bone growth medium into the surgical site which is usually uneven in shape and depth. The surgeon will take the putty on a spatula or other instrument and trowel it into the site or take it in his/her fingers to shape the bone inducing material into the proper configuration to fit the site being corrected.

[0003] Many products exist to treat this surgical need. One example is autologous bone particles or segments recovered from the patient. When removed from the patient, it is wet and viscous from the associated blood. This works very well to heal the defect but requires significant secondary surgery resulting in lengthening the surgery, extending the time the patient is under anesthesia and increasing the cost. In addition, a significant increase in patient morbidity is attendant in this technique as the surgeon must take bone from a non-involved site in the patient to recover sufficient healthy bone, marrow and blood to perform the defect filling surgery. This leads to significant post-operative pain.

[0004] Another product group involves the use of inorganic materials to provide a matrix for new bone to grow at the surgical site. These inorganic materials include hydroxyapatite obtained from sea coral or derived synthetically. Either form may be mixed with the patient's blood and/or bone marrow to form a gel or a putty. Calcium sulfate or plaster of Paris may be mixed with water to similarly form a putty. These inorganic materials are osteoconductive but are bioinert and do not absorb or become remodeled into natural bone. They consequently remain in place indefinitely as a brittle, foreign body in the patient's tissue

[0005] Allograft bone is a logical substitute for autologous bone. It is readily available and precludes the surgical complications and patient morbidity associated with autologous bone as noted above. Allograft bone is essentially a collagen fiber reinforced hydroxyapatite matrix containing active bone morphogenic proteins (BMP) and can be provided in a sterile form. The demineralized form of allograft bone is naturally both osteoinductive and osteoconductive. The demineralized allograft bone tissue is fully incorporated in the patient's tissue by a well established biological mechanism. It has been used for many years in bone surgery to fill the osseous defects previously discussed.

[0006] It is well known in the art that for several decades surgeons have used a patient's own blood as a vehicle in which to mix the patient's bone chips or bone powder, or demineralized bone powder so as to form a defect filling paste. Blood is a useful carrier because it is available from the bleeding operative site, is non-immunogenic to the patient and contains bone morphogenic proteins which facilitate wound healing through new bone growth. However, stored blood from other patients has the deficiencies that any blood transfusion would have such as blood type compatibility, possibility of transmission of disease and unknown concentration of BMP which are to a great extent dependent upon the age of the donor.

[0007] While blood contains from forty percent (40%) to fifty percent (50%) cell mass, it is a satisfactory carrier for demineralized bone powder because it contains both mono- and polysaccharides which contribute to the blood viscosity and provide the bulk viscosity to the paste created by mixing the bone powder and blood. Specific monosaccharides in blood are glucose at a concentration of 60 - 100mg/100ml (0.1%) and polysaccharides such as hexose and glucosamine at approximately 0.1%. Glucuronic acid is also present at approximately 0.4 - 1.4mg/100ml (average 0.01%).

[0008] The problems inherent with using the patients blood as a carrier for demineralized bone powder are the difficulties of mixing the same at the operating site, the difficulty in obtaining a bone paste consistency which can be easily applied to the surgical area. the guesswork in mixing a usable composition at the site and the problem of having a bone paste or gel which will promote optimum bone replacement growth, not be carried away by the body fluids at the operation site or simply fall out of the bone defect site. In an attempt to solve these and other problems, there have been a number of other attempts using other alternative mixtures and compositions.

[0009] Demineralized allograft bone is usually available in a lyophilized or freeze dried and sterile form to provide for extended shelf life. The bone in this form is usually very coarse and dry and is difficult to manipulate by the surgeon. One solution to use such freeze dried bone has been provided in the form of a gel, GRAFTON®, a registered trademark of Osteotech Inc., which is a simple mixture of glycerol and lyophilized, demineralized bone powder of a particle size in the range of 0.1 cm to 1.2 cm (1000 microns to 12,000 microns) as is disclosed in U.S. Patent Number 5,073,373.

[0010] GRAFTON works well to allow the surgeon to place the allograft bone material at the site. However, the carrier,

glycerol has a very low molecular weight (92 Daltons) and is very soluble in water, the primary component of the blood which flows at the surgical site. Glycerol also experiences a marked reduction in viscosity when its temperature rises from room temperature (typically 22° C in an operating room) to the temperature of the patient's tissue, typically 37°C. This combination of high water solubility and reduced viscosity causes the allograft bone material to be "runny" and to flow away from the site almost immediately after placement; this prevents the proper retention of the bone within the site as carefully placed by the surgeon.

[0011] These problems with GRAFTON gel have been attempted to be resolved by using a much larger particle size of allograft bone, specifically lamellae or slivers of bone created by milling or slicing the bone before mixing it with the glycerol carrier. This improves both the bulk viscosity and the handling characteristics of the mixture but still leaves the problem of the fast rate of dissipation of the carrier and some bone due to the solubility of the glycerol carrier. The larger particles of demineralized bone may also retard the development of new bone by the patient because the large bony lamellae do not pack as well as the smaller grainy particles of bone. This will leave more open space and could lengthen the time required to grow new bone and properly fill the defect. Another deficiency of using the bony lamellae is that the ends of the bony fragments are uneven and when packed into the surgical defect, leave uneven filaments of bone protruding out from the defect which can compromise the healing rate.

[0012] U.S. Patent No. 5,290,558 discloses a flowable demineralized bone powder composition using a osteogenic bone powder with large particle size ranging from about 0.1 to about 1.2 cm. mixed with a low molecular weight polyhydroxy compound possessing from 2 to about 18 carbons including a number of classes of different compounds such as monosaccharides, disaccharides, water dispersible oligosaccharides and polysaccharides.

[0013] Hence, the advantages of using the smaller bone particle sizes as disclosed in the 5,073,373 gel patent were compromised by using bone lamellae in the shape of threads or filaments and retaining the low molecular weight glycerol carrier. This later prior art is disclosed in U.S. Patent Numbers 5,314,476 and 5,507,813 and the tissue forms described in these patents are known commercially as the GRAFTON Putty and Flex, respectively.

[0014] The use of the very low molecular weight glycerol carrier also requires a very high concentration of glycerol to be used to achieve the bulk viscosity. Glycerol and other similar low molecular weight organic solvents are toxic and irritating to the surrounding tissues. Furthermore glycerol has been reported to be specifically neurotoxic and this problem is compounded when the concentration of glycerol is at the 20 - 95% level as disclosed in the 5,073,373 patent.

[0015] Another attempt to solve the bone composition problem is shown in U. S. Patent No. 4,172,128 which discloses demineralized bone material mixed with a carrier to reconstruct tooth or bone material by adding a mucopolysaccharide to a mineralized bone colloidal material. The composition is formed from a demineralized coarsely ground bone material, which may be derived from human bones and teeth, dissolved in a solvent forming a colloidal solution to which is added a physiologically inert polyhydroxy compound such as mucopolysaccharide or polyuronic acid in an amount which causes orientation when hydrogen ions or polyvalent metal ions are added to form a gel. The gel will be flowable at elevated temperatures above 35°C and will solidify when brought down to body temperature. Example 25 of the patent notes that mucopolysaccharides produce pronounced ionotropic effects and that hyaluronic acid is particularly responsible for spatial cross-linking. Unfortunately this bone gel is difficult to manufacture and requires a premolded gel form.

[0016] U.S. Patent No. 4,191,747 teaches a bone defect treatment with coarsely ground, denatured bone meal freed from fat and ground into powder. The bone meal is mixed with a polysaccharide in a solution of saline and applied to the bone defect site.

[0017] Another prior art product is the formulation of demineralized allograft bone particles in collagen. Both bovine and human collagen have been used for this application. Bovine collagen carries the risk of an immunogenic reaction by the recipient patient. Recently, it has been found that a disease of cattle, bovine spongioform encephalopathy (BSE) is transmitted from bovine tissue to humans. Thus, bovine tissue carries a risk of disease transmission and is not a desirable carrier for allograft tissue.

[0018] Human collagen is free of these animal based diseases. However, collagen absorbs slowly in the human body, particularly in a bony site with usually a low degree of vascularity. The slow absorption of collagen can delay the growth of new bone and result in the formation of scar tissue at the site. This could result in a non-bony healing and a result with much less tensile strength.

[0019] Accordingly, the prior art as embodied in the glycerol and other carrier based technology to deliver demineralized allograft bone to a surgical osseous site is replete with problems and only partially addresses the problems inherent in the correcting surgical defects.

SUMMARY OF THE INVENTION

[0020] A bone putty with a useful bulk viscosity has been achieved by using a sodium hyaluronate having a molecular weight of from six hundred and ninety thousand to three million Daltons. Preferably the aqueous solution comprises a sodium chloride based phosphate buffer which avoids the toxic problems with the high concentrations of the low mo-

lecular weight organic solvents of the prior art.

[0021] According to the present invention there is provided a sterile malleable bone composition for application to a bone defect site to promote new bone growth at the site comprising a mixture of demineralized osteogenic bone powder, in a hydrogel carrier;

the bone powder having a particle size of from about 100 to about 850 microns;
the bone powder comprising from about 25 to about 35% of the weight of the composition;
the carrier being sodium hyaluronate in an aqueous solution, the sodium hyaluronate having a high molecular weight ranging from six hundred and ninety thousand to three million Daltons and ranging from 1% to 4.5% by weight of the carrier solution.
It can thus be seen that the prior art has attempted to replicate putty/gel obtained by the mixing of blood with bone particles without the necessity of mixing the two together at the surgical site in non-controlled proportions and under time and space prohibitions.

[0022] The selection of high molecular weight sodium hyaluronate allows the use of the preferred small particle size granules of demineralized allograft bone. These small particles pack better in the wound defect and absorb more quickly thereby allowing the bone defect to be remodelled into the natural bone of the patient.

[0023] By use of the present invention one or more of the following advantages may be achieved:-

(i) utilization of demineralized powdered bone in a particle size that is useful to achieve the malleability characteristics that maximizes the amount of bone in the formulation without creating a gritty, less malleable characteristic.
(ii) a non toxic carrier for the bone particles which will not adversely impact on the patient.
(iii) a bone defect material which can be easily handled by the physician and does not degenerate when contacting blood flow at the surgical site.

[0024] In some embodiments of the invention a calcium salt is used with the demineralized bone composition to aid in healing at the bone defect site.

[0025] In other embodiments the invention provides a premixed bone putty/gel in an oxygen protected carrier to keep the putty/gel from drying out or being degraded.

DESCRIPTION OF THE INVENTION

[0026] The present invention is directed towards a demineralized bone powder composition to heal bone defects. The preferred embodiment of Examples I and II are the best mode for the Sodium Hyaluronate putty composition and Examples IV or V for the Sodium Hyaluronate gel composition. These and other alternate embodiments of the invention overcome the two basic deficiencies of the glycerol carrier and bone particle flowable compositions used in the prior art: first, the low molecular weight of glycerol; and second, the use of large particle or lamellae to achieve the preferred bulk viscosity. The types of demineralized bone used in the invention are cortical and corticocancellous bone powder.

[0027] Surprisingly, the combination of the 100 - 420 micron particle size of demineralized, lyophilized, allograft bone when mixed with very low concentrations of these very high molecular weight hydrogels in a suitable carrier produces a malleable putty with clinically useful bone inducing properties. The malleable property permits the surgeon to shape the quantity of bone putty or gel to exactly fit the surgical defect. Manipulation of the "lump" of bone putty may be done without it sticking to the gloves of the surgeon, behaving somewhat like a wet clay used in sculpting.

[0028] The ideal carrier for the malleable putty is a Sodium Hyaluronate having a molecular weight of about 7.0×10^5 to 3.0×10^6 Daltons.

[0029] The molecular weight of the material used in the carrier set forth in the Examples Is (1.2×10^6 Daltons).

[0030] Demineralized, lyophilized allograft bone of particle size of about 100 to about 420 microns at a concentration of about 30% to 35% w/w is mixed into an isotonic saline solution of 2% hyaluronic acid of an average molecular weight of about 1.2 million Daltons and produces a highly desirable malleable bone putty. Hyaluronic acid is generally described as an acid mucopolysaccharide. It is envisioned that suitable amounts of bone morphogenic proteins (BMP) can be added to either the gel or putty at any stage in the mixing process to induce accelerated healing at the bone site. BMP directs the differentiation of pluripotential mesenchymal cells into osteoprogenitor cells which form osteoblasts. The ability of freeze dried demineralized cortical bone to transfer this bone induction principle using BMP present in the bone is well known in the art. However the amount of BMP varies in the bone depending on the age of the bone donor and the bone processing. Sterilization is an additional problem in processing human bone for medical use as boiling, autoclaving and irradiation over 2.0 mrads is sufficient to destroy or alter the BMP present in the bone matrix.

[0031] After conducting numerous experiments it was found that a gel product with optimal formability and handling properties would have a molecular weight ranging from 690,000 to 1,200,000 Daltons with a Sodium Hyaluronate

concentration ranging from 0.75 - 2.0% with a bone concentration ranging from 25 - 27% with a particle size of 100 - 820 microns. This resulted in HA solution viscosities ranging from 1,800 cps to 13,000 cps. It was also found that a putty product with optimal formability and handling properties would have a molecular weight ranging from 690,000 to 1,200,000 Daltons with a Sodium Hyaluronate concentration ranging from 2.0 - 4.5% with a bone concentration ranging from 30 - 33% with a particle size of 100 - 820 microns. This resulted in HA solution viscosities ranging from 6,000 cps to 275,000 cps. It was found that as the viscosity increases, penetration decreases and when the viscosity is the same the increase in percentage of bone particle weight results in a decrease of penetration.

[0032] Another embodiment of the invention is to induce the presence of soluble calcium at the bone defect site. This will encourage new bone growth through the normal biochemical mechanism. Soluble calcium can be attracted to the surgical site by using a sodium phosphate buffer of pH 6.8 to 7.2 in lieu of the isotonic saline. The phosphate buffer will attract calcium cations to the site from the surrounding healthy bone and create an equilibrium concentration of the calcium precisely at the site of healing where it is most desirable to grow new bone.

[0033] Any number of medically useful substances can be used in the invention by adding the substances to the composition at any steps in the mixing process or directly to the final composition. Such substances include collagen and insoluble collagen derivatives, hydroxy apatite and soluble solids and/or liquids dissolved therein. Also included are antiviricides such as those effective against HIV and hepatitis; antimicrobial and/or antibiotics such as erythromycin, bacitracin, neomycin, penicillin, polymyxin B, tetracycline, viomycin, chloromycetin and streptomycin, cefazolin, ampicillin, azactam, tobramycin, clindamycin and gentamycin. It is also envisioned that amino acids, peptides, vitamins, co-factors for protein synthesis; hormones; endocrine tissue or tissue fragments; synthesizers; enzymes such as collagenase, peptidases, oxidases; polymer cell scaffolds with parenchymal cells; angiogenic drugs and polymeric carriers containing such drugs; collagen lattices; biocompatible surface active agents, antigenic agents; cytoskeletal agents; cartilage fragments, living cells such as chondrocytes, bone marrow cells, mesenchymal stem cells, natural extracts, tissue transplants, bioadhesives, transforming growth factor (TGF-beta), insulin-like growth factor (IGF-1); growth hormones such as somatotropin; bone digestors; antitumor agents; fibronectin; cellular attractants and attachment agents; immuno-suppressants; permeation enhancers, e.g. fatty acid esters such as laureate, myristate and stearate monoesters of polyethylene glycol, enamine derivatives, alpha-keto aldehydes can be added to the composition.

[0034] The invention can be further understood by the following examples with the percentages being determined by weight. In some samples a penetration test was used to measure the bulk consistency of the formulation. In principle, the test measures the depth of penetration of a metal cone of a known mass inserted into a sample of the formulation for a fixed time. The heavier a formulation the less penetration occurs. this test is adopted from ASTM Method D 1403-96: Standard Test Method for Cone preparation Lubricating Grease Using One Quarter and One-Half Scale Cone Equipment. All examples could also be done in an aseptic environment to maintain a sterile final product.

Examples of the Invention

[0035] In the examples the molecular weight of the various carrier components used is as follows_

1) Sodium Hyaluronate 1.2×10^6 - 2.6×10^6 Daltons

Example I:

[0036] A malleable putty of 2% solution Hyaluronic Acid in isotonic saline with 250-420 micron cortical allograft bone powder @ 30%.

[0037] 502 milligrams of freeze dried cortical allograft bone of particle size ranging from 250 - 420 microns was mixed into 1,170 milligrams of a 2% solution of sodium hyaluronate in isotonic saline. The bone component is added to achieve a bone concentration of 30% (w/w). The solution was well mixed and allowed to stand for 2-3 hours at room temperature to provide a malleable putty with excellent formability properties.

[0038] 528 milligrams of freeze dried cortical allograft bone of particle size of 420-850 microns was mixed into 522 milligrams of a 20% solution of Pluronic F108 in isotonic saline. The bone component is added to achieve a bone concentration of 50%(w/w). The solution was well mixed and allowed to stand for 2-3 hours at room temperature. This provided a putty with poor formability properties.

Example II:

[0039] A malleable putty of 3% solution hyaluronic acid with 100-300 micron cortical allograft bone powder @ 33%.

[0040] 720 milligrams of freeze dried cortical allograft bone of particle size of 100-300 microns was mixed into 1,402 milligrams of a 3% solution of sodium hyaluronate in an aqueous solution of a sodium chloride based phosphate buffer having a viscosity within the range of from about 230,000 cps to about 275,000 cps. The bone component is added to

achieve a bone concentration of 33% (w/w). The solution was well mixed and allowed to stand for 2-3 hours at room temperature. This provided a malleable putty with excellent formability properties.

Example III:

[0041] A malleable putty of 1% solution hyaluronic acid with 250-420 micron cortical allograft bone powder @ 40%.
[0042] 605 milligrams of freeze dried cortical allograft bone of particle size of 250-420 microns was mixed into 906 milligrams of a 1% solution of sodium hyaluronate in isotonic saline. The bone component was added to achieve a bone concentration of 40%(w/w). The solution was well mixed and allowed to stand for 2-3 hours at room temperature. This provided a malleable putty with poor formability properties.

Example IV

[0043] A flowable gel of 250 - 420 micron particle size cortical allograft bone granules in a 1% solution of Hyaluronic Acid at a 25% (w/w) of bone content.
[0044] 503 milligrams of allograft freeze dried cortical bone was mixed into 1,502 milligrams of a 1% solution of sodium hyaluronate having a viscosity within the range of from 2,000 cps to 6,000 cps in an aqueous solution of a sodium chloride based phosphate buffer. The solution was well mixed and allowed to stand at room temperature to provide a flowable gel.

Example V:

[0045] A flowable gel of 250-420 micron particle size cortical allograft granules in a 1% solution of Hyalumonic Acid at a 30% (w/w) of bone content.
[0046] 501 milligrams of allograft freeze dried cortical bone was mixed into 1,167 milligrams of a 1% solution of sodium hyaluronate in isotonic saline. The bone component is added to achieve a bone concentration of 30%(w/w). The solution was well mixed and allowed to stand for 2-3 hours at room temperature. This provided a flowable gel.

Example VI:

[0047] A flowable gel of 420-850 micron particle size cortical allograft granules in a 1% solution of hyaluronic acid at a 25%(w/w) of bone content.
[0048] 501 milligrams of allograft freeze dried cortical bone was mixed into 1,501 milligrams of a 1% solution of sodium Hyaluronate in isotonic saline. The bone component is added to achieve a bone concentration of 25%(w/w). The solution was well mixed and allowed to stand for 2-3 hours at room temperature. This provided a flowable gel.

Example VII:

[0049] A flowable gel of 420-850 micron particle size cortical allograft granules in a 1% solution of hyaluronic acid at a 30%(w/w) of bone content.
[0050] 500 milligrams of allograft freeze dried cortical bone was mixed into 1,166 milligrams of a 1% solution of sodium hyaluronate in isotonic saline. The bone component is added to achieve a bone concentration of 30%(w/w). The solution was well mixed and allowed to stand for 2-3 hours at room temperature. This provided a flowable gel.
[0051] The following Table I sets forth the above noted examples I - VII in comparative form:

Table 1

Example#	Ref #	Carrier Solution	Bone mg/ Carrier mg	Bone %	Particle Size (micron)	Comments	Putty/Gel
I	4.2	2% HA	502mg/1170 mg	30	250-420	good	putty: excellent formability
II	7a7	3% HA	720 mg/1402 mg	33	100-300	good consistency: slightly sticky and slightly dry	putty: excellent formability
III	2-6	1% HA	605 mg/906 mg	40	250-420	too grainy; very dry	putty: poor formability
IV	5-1	1% HA	503 mg/1502 mg	25	250-420	wet, still good consistency and formability: very moderately grainy	flowable gel
V	5-2	1% HA	501 mg/1167 mg	30	250-420	drier than 5-1, reasonable formability; much grainier	flowable gel
VI	5-4	1% HA	501 mg/1501 mg	25	420-850	wet, grainy: not formable. may be flowable	flowable gel
VII	5-5	1% HA	500 mg/1166 mg	30	420-850	wet, formable, grainy	flowable gel

In summation, it can been seen from Table I that:

[0052] A flowable gel can be made up of about 25-30% bone powder (particle size in a range of 250-850 microns) mixed into a high molecular weight hydrogel carried in solution, such as 1% sodium hyaluronate (Examples IV, V, VI, VII).

[0053] A putty with good formability can be made up of about 30-40% of bone powder (particle size in a range of 100-850 microns) mixed into a hydrogel solution, such as a 2-3% sodium hyaluronate or 3% chitosan (Examples I and II

[0054] Examples III of test results did not produce either a successful flowable gel or putty. These show the limits of the concentrations of the respective examples. Particle sizes below about 100 microns will absorb too quickly.

[0055] In order to preclude oxidation degradation and loss of viscosity the composition should be mixed and packaged in an oxygen free environment. The mixing of the demineralized bone powder into hydrogel solution is undertaken in an enclosed sterile glove chamber with an oxygen free environment such as in a nitrogen, argon or other inert gas filled chamber. The mixed malleable bone composition is then placed in a sterile container such as an impervious syringe barrel or vial, sealed and placed in a sterile sealed package which is filled with an inert gas or vacuum sealed.

[0056] The principles, preferred embodiments and modes of operation of the present invention have been described in the foregoing specification. However, the invention should not be construed as limited to the particular embodiments which have been described above. Instead, the embodiments described here should be regarded as illustrative rather than restrictive. Variations and changes may be made by others without departing from the scope of the present invention as defined by the following claims:

Claims

1. A sterile malleable bone composition for application to a bone defect site to promote new bone growth at the site comprising a mixture of demineralized osteogenic bone powder, in a hydrogel carrier;

   the bone powder having a particle size of from about 100 to about 850 microns;
   the bone powder comprising from about 25 to about 35% of the weight of the composition;
   the carrier being sodium hyaluronate in an aqueous solution, the sodium hyaluronate having a high molecular weight ranging from six hundred and ninety thousand to three million Daltons and ranging from 1% to 4.5% by weight of the carrier solution.

2. A sterile malleable bone composition as claimed in claim 1, wherein said mixture includes bone morphogenic proteins in excess of the amount naturally occurring in allogenic bone.

3. A sterile malleable bone composition as claimed in claim 1 or 2, wherein the aqueous solution comprises a sodium chloride based phosphate buffer.

4. A sterile malleable bone composition as claimed in any one of the preceding claims, wherein said bone powder is cortical allograft bone powder or corticocancellous allograft bone powder.

5. A sterile malleable bone composition as claimed in any one of the preceding claims, which is a putty composition, in which said bone powder is demineralized lyophilized allograft bone powder and said carrier comprises an aqueous solution of a sodium salt of hyaluronic acid hydrogel, the hyaluronic acid component ranging from 1 to 4.5% by weight of the carrier solution and having a molecular weight of at least 10^6 Daltons and a viscosity ranging from 6,000 to about 275,000 cps.

6. A sterile malleable bone putty composition as claimed in claim 5 wherein said hydrogel carrier has a 2 -3% hyaluronic acid concentration with the balance of the carrier formulation containing a sodium phosphate buffer with a pH of 6.8 to 7.2, said buffer attracting calcium and concentrating same at the bone defect site.

7. A sterile malleable bone putty composition as claimed in claim 5 or 6, including antimicrobial and/or antibiotics such as erythromycin, bacitracin, neomycin penicillin, polymyxin B, tetracycline, viomycin, chloromycetin and streptomycin, cefazolin, ampicillin, azactam, tobramycin, clindamycin, gentamycin and vitamins.

8. A sterile malleable bone composition as claimed in any one of claims 1 to 4, which is a putty composition and which comprises bone growth inducing demineralized lyophilized allograft bone powder with a particle size ranging from about 100 to about 420 microns in a sodium hyaluronate, and water carrier, the bone content of the composition ranging from about 30% to about 35% by weight and the high molecular weight sodium hyaluronate component

ranges from 2% to 4.5% by weight of the carrier has a molecular weight greater than one million Daltons.

9. A sterile malleable bone gel composition for application to a bone defect site to promote new bone growth at the side which comprises a new bone growth inducing amount of demineralized lyophilized allograft bone powder with a particle size ranging from about 250 to about 850 microns in a hyaluronic acid in water hydrogel carrier with the hyaluronic acid component comprising abut 1% of the carrier and having a molecular weight over 1.0 x 10^6 Daltons, the bone powder content of the composition ranging from about 25% to about 30%.

10. A sterile malleable bone gel composition as claimed in claim 9, in which said bone powder has a particle size ranging from about 250 to about 420 microns and said carrier having a viscosity of about 1,800 to 13,000 cps.

11. A composition as claimed in claim 9 or 10 wherein the aqueous solution comprises a sodium chloride based buffer.

12. A composition as claimed in any one of claims 5 to 10 wherein said bone powder includes added bone morphogenic proteins.

13. A composition as claimed in any one of the preceding claims, wherein the composition includes living cells such as chondrocytes, bone marrow cells or mesenchymal stem cells.

Patentansprüche

1. Sterile verformbare Knochenzusammensetzung zur Anwendung an einer Stelle des Knochendefekts zur Förderung neuen Knochenwachstums an der Stelle, umfassend ein Gemisch aus demineralisiertem osteogenem Knochenpulver in einem Hydrogelträger;
wobei das Knochenpulver eine Partikelgröße von ca. 100 bis ca. 850 Mikron aufweist;
wobei das Knochenpulver von ca. 25 bis ca. 35 Gew.-% der Zusammensetzung umfasst;
wobei der Träger Natriumhyaluronat in einer wässrigen Lösung darstellt, wobei das Natriumhyaluronat ein hohes Molekulargewicht im Bereich von 690 000 bis 3 000 000 Dalton aufweist und im Bereich von 1 Gew.-% bis 4,5 Gew.-% bezogen auf die Trägerlösung liegt.

2. Sterile verformbare Knochenzusammensetzung nach Anspruch 1, worin genanntes Gemisch morphogene Knochenproteine über die Menge hinausgehend einschließt, die im allogenen Knochen natürlich vorkommt.

3. Sterile verformbare Knochenzusammensetzung nach Anspruch 1 oder 2, worin die wässrige Lösung einen auf Natriumchlorid basierenden Phosphatpuffer umfasst.

4. Sterile verformbare Knochenzusammensetzung nach einem der vorangehenden Ansprüche, worin genanntes Knochenpulver kortikales Allograft-Knochenpulver oder kortikospongiöses Allograft-Knochenpulver darstellt.

5. Sterile verformbare Knochenzusammensetzung nach einem der vorangehenden Ansprüche, welche eine Kittzusammensetzung darstellt, worin genanntes Knochenpulver demineralisiertes, lyophilisiertes Allograft-Knochenpulver darstellt und genannter Träger eine wässrige Lösung eines Natriumsalzes des Hyalyronsäure-Hydrogels umfasst, wobei die Hyaluronsäurekomponente im Bereich von 1 bis 4,5 Gew.-% bezogen auf die Trägerlösung liegt und ein Molekulargewicht von mindestens 10^6 Dalton und eine Viskosität im Bereich von 6 000 bis ca. 275 000 cps aufweist.

6. Sterile verformbare Knochenkittzusammensetzung nach Anspruch 5, worin genannter Hydrogelträger eine 2 - 3%ige Hyaluronsäure-Konzentration aufweist, wobei der Rest der Trägerformulierung einen Natrium-Phosphatpuffer mit einem pH von 6,8 bis 7,2 enthält, wobei genannter Puffer Kalzium anzieht und dasselbe an der Stelle des Knochendefekts konzentriert.

7. Sterile verformbare Knochenkittzusammensetzung nach Anspruch 5 oder 6, einschließlich antimikrobieller Mittel und/oder Antibiotika, wie zum Beispiel Erythromycin, Bacitracin, Neomycin, Penicillin, Polymyxin B, Tetracyclin, Viomycin, Chloromycetin und Streptomycin, Cefazolin, Ampicillin, Azactam, Tobramycin, Clindamycin, Gentamycin und Vitaminen.

8. Sterile verformbare Knochenzusammensetzung nach einem der Ansprüche 1 bis 4, die eine Kittzusammensetzung

darstellt und die Knochenwachstum induzierendes demineralisiertes lyophilisiertes Allograft-Knochenpulver mit einer Partikelgröße im Bereich von ca. 100 bis ca. 420 Mikron in einem Natriumhyaluronat und einen Wasserträger umfasst, wobei der Knochengehalt der Zusammensetzung, der im Bereich von ca. 30 Gew.-% bis ca. 35 Gew.-% liegt und die Natriumhyaluronatkomponente mit hohem Molekulargewicht, die im Bereich von 2 Gew.-% bis 4,5 Gew.-% bezogen auf den Träger liegt, ein Molekulargewicht aufweist, das größer als 1 000 000 Dalton ist.

9. Sterile verformbare Knochengelzusammensetzung zur Anwendung an einer Stelle des Knochendefekts zur Förderung neuen Knochenwachstums an der Stelle, die eine neue Knochenwachstum induzierende Menge von demineralisiertem lyophilisiertem Allograft-Knochenpulver mit einer Partikelgröße im Bereich von ca. 250 bis ca. 850 Mikron in einer Hyaluronsäure in einem wässrigen Hydrogelträger umfasst, wobei die Hyaluronsäurekomponente ca. 1 % des Trägers umfasst und ein Molekulargewicht über 1,0 x 10^6 Dalton aufweist, wobei der Knochenpulvergehalt der Zusammensetzung im Bereich von ca. 25 % bis ca. 30 % liegt.

10. Sterile verformbare Knochengelzusammensetzung nach Anspruch 9, worin genanntes Knochenpulver eine Partikelgröße im Bereich von ca. 250 bis ca. 420 Mikron aufweist und wobei genannter Träger eine Viskosität von ca. 1 800 bis 13 000 cps aufweist.

11. Zusammensetzung nach Anspruch 9 oder 10, worin die wässrige Lösung einen auf Natriumchlorid basierenden Puffer umfasst.

12. Zusammensetzung nach einem der Ansprüche 5 bis 10, worin genanntes Knochenpulver hinzugefügte morphogene Knochenproteine einschließt.

13. Zusammensetzung nach einem der vorangehenden Ansprüche, worin die Zusammensetzung lebende Zellen, wie zum Beispiel Chondrozyten, Knochenmarkzellen oder mesenchymale Stammzellen einschließt.

Revendications

1. Composition osseuse malléable stérile pour application à un site de défect osseux pour promouvoir la croissance osseuse en ce site comprenant un mélange de poudre d'os ostéogène déminéralisé dans un hydrogel porteur ;

   la poudre d'os ayant une taille de particule d'environ 100 à environ 850 microns ;
   la poudre d'os représentant d'environ 25 % à environ 35 % du poids de la composition ;
   le porteur étant le hyaluronate de sodium dans une solution aqueuse, le hyaluronate de sodium ayant un poids moléculaire élevé de six cent quatre-vingt dix mille à trois millions de Daltons et représentant de 1 % à 4,5 % en poids de la solution porteuse.

2. Composition osseuse malléable stérile selon la revendication 1, dans laquelle ledit mélange inclut des protéines morphogènes osseuses dans une quantité supérieure à celle naturellement présente dans l'os allogène.

3. Composition osseuse malléable stérile selon la revendication 1 ou 2, dans laquelle la solution aqueuse comprend un tampon phosphate à base de chlorure de sodium.

4. Composition osseuse malléable stérile selon l'une quelconque des revendications précédentes, dans laquelle ladite poudre d'os est une allogreffe qui est une poudre d'os cortical ou une allogreffe qui est une poudre d'os cortico-spongieux.

5. Composition osseuse malléable stérile selon l'une quelconque des revendications précédentes, qui est une composition pour comblement, dans laquelle ladite poudre d'os est une allogreffe qui est une poudre d'os lyophilisé déminéralisé et ledit porteur comprend une solution aqueuse d'un sel de sodium d'hydrogel d'acide hyaluronique, l'acide hyaluronique représentant de 1 % à 4,5 % en poids de la solution porteuse et ayant un poids moléculaire d'au moins 10^6 Daltons et une viscosité de 6.000 à environ 275.000 cps.

6. Composition osseuse malléable stérile pour comblement selon la revendication 5, dans laquelle ledit hydrogel porteur a une concentration en acide hyaluronique de 2 % à 3 %, le reste de la formulation du porteur contenant un tampon phosphate de sodium avec un pH de 6,8 à 7,2, ledit tampon attirant et concentrant le calcium en le site du défect osseux.

7. Composition osseuse malléable stérile pour comblement selon la revendication 5 ou 6, incluant des agents antimicrobiens et/ou des antibiotiques tels que l'érythromycine, bacitracine, néomycine, pénicilline, polymyxine B, tétracycline, viomycine, chloromycétine et streptomycine, céfazoline, ampicilline, azactame, tobramycine, clindamycine, gentamycine et des vitamines.

8. Composition osseuse malléable stérile selon l'une quelconque des revendications 1 à 4, qui est une composition pour comblement et qui comprend une allogreffe qui est une poudre d'os lyophilisé déminéralisé induisant une croissance osseuse ayant une taille de particule d'environ 100 à environ 420 microns dans un porteur de hyaluronate de sodium et d'eau, la teneur en os de la composition étant d'environ 30 % à environ 35 % en poids et le hyaluronate de sodium de poids moléculaire élevé représentant de 2 % à 4,5 % en poids du porteur a un poids moléculaire supérieur à un million de Daltons.

9. Composition osseuse malléable stérile en gel pour application à un site de défect osseux pour promouvoir la croissance osseuse en ce site qui comprend une quantité d'allogreffe qui est une poudre d'os lyophilisé déminéralisé induisant une croissance osseuse avec une taille de particule d'environ 250 à environ 850 microns dans un hydrogel porteur d'acide hyaluronique et d'eau, l'acide hyaluronique représentant environ 1 % du porteur et ayant un poids moléculaire supérieur à $1,0 \times 10^6$ Daltons, la teneur en poudre d'os de la composition étant d'environ 25 % à environ 30 %.

10. Composition osseuse malléable stérile en gel selon la revendication 9, dans laquelle ladite poudre d'os a une taille de particule d'environ 250 à environ 420 microns et ledit porteur a une viscosité d'environ 1.800 à 13.000 cps.

11. Composition selon la revendication 9 ou 10, dans laquelle la solution aqueuse comprend un tampon à base de chlorure de sodium.

12. Composition selon l'une quelconque des revendications 5 à 10, dans laquelle ladite poudre d'os inclut des protéines morphogènes osseuses ajoutées.

13. Composition selon l'une quelconque des revendications précédentes, dans laquelle la composition inclut des cellules vivantes telles que chondrocytes, cellules de moelle osseuse ou cellules souches mésenchymales.